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ART UNIT	PAPER NUMBER
1644	9

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,971	AHOTUPA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *7-16,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-20 are pending.

2. Applicant's election with traverse of Group 1, Claims 1-6 (now claims 1-6 and 17-18) drawn to a method of inhibiting overactivity of phagocytes or lymphocytes by administering a lignan wherein the lignan is hydroxymatairesinol, filed 4/17/03, is acknowledged. The traversal is on the grounds that (1) hydroxymatairesinol, matairesinol and enterolactone are structurally related, (2) The field of search includes only two classes and there is no serious burden on the Examiner if restriction is required, (3) the search of each of the alleged 127 inventions is identical and can be made without serious burden. Upon reconsideration, Groups 2-6 have been rejoined with Group I. Therefore, the requirement of Group 1 (now claims 1-6 and 17-18) and Groups 7-127 is still deemed proper and is therefore made FINAL.

3. Claims 7-16 and 19-20 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-6 and 17-18, drawn to a method of inhibiting overactivity of phagocytes or lymphocytes by administering a lignan wherein the lignan is hydroxymatairesinol, matairesinol, enterolactone or a mixture of said ligans are being acted upon in this Office Action.

5. Claim 1 is objected to because the article "A" is missing; said claim should have been "A method" instead of "Method of ...".

6. The disclosure is objected to because of the following informalities: (1) "enterolactone (III and IV) or Matairesinol (V and VI)" on page 10 line 18 does not match the results shown in Figure 3. According to the Figure 3, Matairesinol is panel (III and IV) or Enterolactone (V and VI). Which one (the specification or the labeling of the Figure 3) is correct? (2) The labeling of Fig 4A and Fig 4B where "Kontr" should have been "control". Appropriate action is required.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-6 and 17-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of inhibiting oxidative burst in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, and wherein the phagocytes are neutrophils, (2) a method of inhibiting myeloperoxidase activity in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, and wherein the phagocytes are macrophages, and (3) a method of inhibiting Fas induced apoptosis in lymphocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, matairesino or enterolactone, and wherein the lymphocytes are T lymphocytes, **does not** reasonably provide enablement for (1) *any* method as set forth in claims 1-6 and 17-18 for treating *any* disease such as ischemia reperfusion injury wherein the injury is myocardial infraction, stroke, transplantation, adult respiratory distress syndrome, ischemic heart disease, enterotoxic or hemorrhagic shock, or any chronic condition such as rheumatoid arthritis, any allergic condition including asthma, any inflammatory condition such as inflammatory bowel disease or skin, HIV, AIDS, psoriasis, Parkinson's disease, Alzheimer's disease, any autoimmune disease such as type I or type II diabetes, hypercholesterolemic arteriosclerosis, cataract or amylotrophic lateral sclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only (1) a method of inhibiting oxidative burst in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is

hydroxymatairesinol, and wherein the phagocytes are neutrophils, (2) a method of inhibiting myeloperoxidase activity in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, and wherein the phagocytes are macrophages, and (3) a method of inhibiting Fas induced apoptosis in lymphocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, matairesino or enterolactone, and wherein the lymphocytes are T lymphocytes.

The specification does not teach how to use *any* lignan such as hydroxymatairesinol, matairesinol, enterolactone or a mixture thereof for inhibiting the overactivity of any phagocytes or lymphocytes in any individual for treating any disease because there is insufficient guidance as to the mixture of hydromatairesinol and matairesinol for inhibiting any overactivity of neutrophils such as oxidative burst. In fact the specification shows on page 9, Table 1 that the IC50 of matairesinol for oxidative burst is 11 and the IC50 of hydroxymatairesinol is 5.3 as compared to the 4-OH-toremifen, which is the inhibitor of oxidative burst that has an IC50 value of 1.7. The extent of inhibition by matairesinol is marginal at best. Further, there are no showing that the mixture of hydromatairesinol and matairesinol is effective for inhibiting any overactivity of neutrophils such as oxidative burst in vitro, much less in vivo, in turn, for treating any disease.

With regard to the method of inhibiting overactivity of phagocytes wherein the phagocytes are myeloid origin in an individual by administering to said individual any lignan wherein the lignan is matairesinol, or a mixture thereof of enterolactone and hydroxymatairesinol, the specification shows on page 9, Table 1 that the IC50 of matairesinol for myeloperoxidase activity is 44.5 and the IC50 of hydroxymatairesinol is 6.8 as compared to the Nitecapone, which is the inhibitor of myeloperoxidase activity, that has a IC50 value of 2.3. Based on these results, it is not clear if Matairesinol could inhibit myeloperoxidase activity as claimed in the absence of a negative control. Further, there are no showings that the mixture of enterolactone and hydroxymatairesinol is effective for inhibiting any inhibiting overactivity of phagocytes that are myeloid origin such as myeloperoxidase activity in converting the reactive oxygen species released by any stimuli.

With regard to of inhibiting Fas induced apoptosis in T lymphocytes by administering an effective amount of a lignan in an individual wherein the lignan is hydroxymatairesinol, matairesino or enterolactone or "a mixture thereof", there are no vivo working example that administering to any individual *any* lignan mentioned above is effective for treating any disease.

Pool-Zobel *et al* teach that lignan such as enterolactone reduces oxidized bases at high, non-physiological concentrations but had no effects on oxidative stress (See page 1251, column 2, last paragraph, Fig 4 and 5, in particular).

A method of inhibiting overactivity of phagocytes or lymphocyte in an individual in the absence of in vivo data are unpredictable for the following reasons: (1) the lignan or lignans mentioned above may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the lignan; (2) the lignan may not reach the target area because, i.e. the lignan may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the lignan unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering any lignan such as hydroxymatairesinol, matairesino or enterolactone or a mixture thereof. The specification does not teach how to extrapolate data obtained from in vitro oxidative burst and myeloperoxidative assays to the development of a method of inhibiting "overeactivity of phagocytes or lymphocytes", commensurate in scope with the claimed invention.

The Merck manual does not recognize the use of *any* lignan such as hydroxymatairesinol, matairesino or enterolactone or a mixture thereof for inhibiting the overactivity of phagocytes or lymphocytes such as oxidative burst, myeloperoxidase activity, in turn, to treat, or to prevent any disease (See page 420-421, in particular). A person of skill in the art could not predict which particular lignan such as hydroxymatairesinol, matairesino or enterolactone or "a mixture thereof" from which plant are effective for inhibiting overactivity of phagocytes or lymphocytes to treat or to prevent which disease. Even if the method is limited to in vitro, the specification discloses that not all lignans have the same properties such as inhibiting oxidative burst in neutrophils or inhibiting myeloperoxidase activity (See page 9, Table 1). Although some of the activities of lignans have been shown in vitro, the relevance of these studies to in vivo disease is not known. In view of the lack of guidance and the lack of predictability of structure-activity difference among three different lignans with respect to the specific oxidative burst, and myeloid peroxidase activity, much less to inhibiting overactivity of phagocytes or lymphocytes in vivo to treat or to prevent any disease, the lack of established clinical protocols for effective lignan based therapies

for any disease such as such as ischemia reperfusion injury wherein the injury is myocardial infraction, stroke, transplantation, adult respiratory distress syndrome, ischemic heart disease, enterotoxic or hemorrhagic shock, or any chronic condition such as rheumatoid arthritis, any allergic condition including asthma, any inflammatory condition such as inflammatory bowel disease or skin, HIV, AIDS, psoriasis, Parkinson's disease, Alzheimer's disease, any autoimmune disease such as type I or type II diabetes, hypercholesterolemic arteriosclerosis, cataract or amylotrophic lateral sclerosis, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

9. Claims 1-6 and 17-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any method of inhibiting overactivity of phagocytes or lymphocytes in any individual by administering *any* lignan such as hydroxymatairesinol, matairesinol, enterolactone or a mixture thereof as set forth in claims 1-6, 17 and 18 to treat or to prevent *any* disease such as ischemia reperfusion injury wherein the injury is myocardial infraction, stroke, transplantation, adult respiratory distress syndrome, ischemic heart disease, enterotoxic or hemorrhagic shock, or any chronic condition such as rheumatoid arthritis, any allergic condition including asthma, any inflammatory condition such as inflammatory bowel disease or skin, HIV, AIDS, psoriasis, Parkinson's disease, Alzheimer's disease, any autoimmune disease such as type I or type II diabetes, hypercholesterolemic atherosclerosis, cataract or amylotrophic lateral sclerosis.

The specification discloses only (1) a method of inhibiting oxidative burst in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, and wherein the phagocytes are neutrophils, (2) a method of inhibiting myeloperoxidase activity in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, and wherein the phagocytes are macrophages, and (3) a method of inhibiting Fas induced apoptosis in lymphocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, matairesino or enterolactone, and wherein the lymphocytes are T lymphocytes.

Other than the specific methods of (1) inhibiting oxidative burst in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, and wherein the phagocytes are neutrophils, (2) inhibiting myeloperoxidase activity in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, and wherein the phagocytes are macrophages, and (3) inhibiting Fas induced apoptosis in lymphocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, matairesino or enterolactone, and wherein the lymphocytes are T lymphocytes, the specification does not adequately describe how to effectively treat or prevent any disease or reach any therapeutic endpoint in any individual by administering any lignan such as hydroxymatairesinol, matairesino or enterolactone or a mixture thereof. The specification does describe how to extrapolate data obtained from in vitro oxidative burst and myeloperoxidative assays to the development of a method of inhibiting "overeactivity of phagocytes or lymphocytes", commensurate in scope with the claimed invention.

Given the lack of any in vivo working examples for inhibiting overactivity of phagocytes or lymphocytes by administering any lignan wherein oxidative burst caused by any stimulus of the neutrophils is decrease, wherein the myeloperoxidase activity in converting the reactive oxygen species, released by oxidative burst caused by stimuli, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. Claims 1-6 and 17-18 are free of prior art.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

13. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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